Journal of Steroid Biochemistry & Molecular Biology xxx (2013) xxx–xxx

Contents lists available at SciVerse ScienceDirect

Journal of Steroid Biochemistry and Molecular Biology

journal homepage: www.elsevier.com/locate/jsbmb

Review

Current status on development of steroids as anticancer agents

Atul Gupta, B. Sathish Kumar, Arvind S. Negi*

Medicinal Chemistry Department, CSIR-Central Institute of Medicinal and Aromatic Plants (CSIR-CIMAP), Kukrail Picnic Spot Road, Lucknow 226015, U.P., India

ARTICLE INFO

Article history:
Received 4 December 2012
Received in revised form 25 April 2013
Accepted 19 May 2013

Keywords:
Antiestrogens
Aromatase inhibitors
Hormone dependent cancers
17β-Hydroxysteroids dehydrogenase inhibitors
Steroid conjugates
Steroid sulfatase inhibitors

ABSTRACT

Steroids are important biodynamic agents. Their affinities for various nuclear receptors have been an interesting feature to utilize them for drug development particularly for receptor mediated diseases. Steroid biochemistry and its crucial role in human physiology, has attained importance among the researchers. Recent years have seen an extensive focus on modification of steroids. The rational modifications of perhydrocyclopentanophenanthrene nucleus of steroids have yielded several important anticancer lead molecules. Exemestane, SR16157, fulvestrant and 2-methoxyestradiol are some of the successful leads emerged on steroidal pharmacophores.

The present review is an update on some of the steroidal leads obtained during past 25 years. Various steroid based enzyme inhibitors, antiestrogens, cytotoxic conjugates and steroidal cytotoxic molecules of natural as well as synthetic origin have been highlighted.

This article is part of a Special Issue entitled 'Synthesis of steroids'.

© 2013 Published by Elsevier Ltd.

Contents

1. Introduction

Carcinogenesis is a highly complex multistep process induced by a number of carcinogens which leads to development of cancer [1]. Depending upon stage of disease and affected body part, there are more than 100 different types of cancer such as oral, lung, breast, uterine and ovary. Cancer cells abnormally divide without control and invade nearby normal cells. Over the period of time, these can move from one organ to another through the blood and lymph systems and damage the healthy cells in different tissues. This stage of disease is known as metastasis. Because of the severity of disease, cancer is now considered one of the social and economic concerns on the public health-care system. Over the years, several anticancer drugs have been developed with excellent cytotoxicity such as paclitaxel and cisplatin. However, owing to their non-selective action these are associated with serious side effects such as bone marrow depression, alopecia and nephrotoxicity. Hence, their use is limited. On the other hand, antiproliferative drug like tamoxifen have receptor based high selective action on cancer cells. However, these agents are not very effective to kill the existing tumour cells and their prolong use may develop uterine

* Corresponding author. Tel.: +91 522 2342676x327; fax: +91 522 2342666.
E-mail addresses: arvindcimap@gmail.com, arvindcimap@rediffmail.com (A.S. Negi).

0960-0760/$ – see front matter © 2013 Published by Elsevier Ltd.
http://dx.doi.org/10.1016/j.jsbmb.2013.05.011

Please cite this article in press as: A. Gupta, et al., Current status on development of steroids as anticancer agents, J. Steroid Biochem. Mol. Biol. (2013), http://dx.doi.org/10.1016/j.jsbmb.2013.05.011

UNCORRECTED PROOF

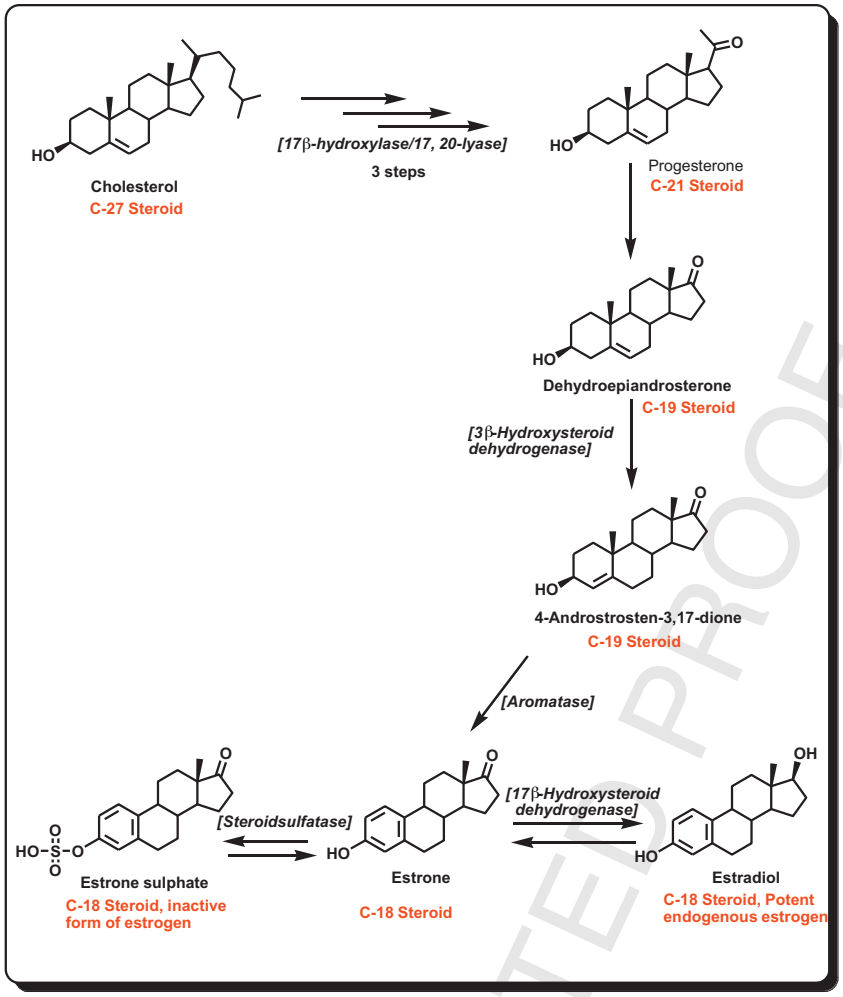

Fig. 1. Schematic presentation of steroidogenesis.

and endometrial cancers. Despite several advances made towards the diagnosis, prevention and cure of cancer, it remains one of the major causes of human morbidity and mortality. Presently, it is second largest killer to human being after cardiovascular disease which accounted 7.6 million deaths in 2008 (13% of total human deaths) and projected to continue rising 13.1 million by 2030 [2]. Therefore, it is a need to have safer and more effective anticancer drug and indeed a challenge for medicinal chemists.

Steroidogenesis and its effect on human physiology has been most fascinating aspect to Biochemists and Endocrinologists. Various types of steroid molecules are synthesized biochemically in human body involving conversion of cholesterol (C27) into progestins (C21) followed by androgens (C19) and finally into estrogens (C18) with the help of various enzymes (Fig. 1). This multistep process is known as steroidogenesis [3]. As described above cholesterol is the main source of steroids in ovaries. Enzymes such as aromatase (CYP450arom), 17β-hydroxysteroid dehydrogenase (17β-HSDs) are essentially required in the last step of estrogen biosynthesis while steroid sulfatase (STS) is required for interconversion from inactive form of estrogen to their active form. Various important steroid hormones are synthesized by this process such as progestins, androgens, estrogens, glucocorticoids and mineralocorticoids.

Among these hormones, biosynthesized from cholesterol, estrogens are the main hormone responsible for the maintenance of Central Nervous System (CNS), Cardiovascular system (CVS) and bones in both males and females in general and development of secondary sexual characteristics in females in particular. Steroid hormone related carcinogenesis is mainly due to accelerated cell proliferation. These metabolizing enzymes and steroidal receptors are major players. Estrogens also play a crucial role in the cell proliferation. However, over-expression of estrogens stimulate excess proliferation of hormone sensitive cells leading to various types of hormone dependent cancer such as breast, uterine, ovarian, prostate and endometrial cancers [4]. Some of the cancers are due to rise in reductive activity and decrease in oxidative activity towards the estrogens and androgens. Nevertheless, steroids have been centre of research for the development of antihormonal drugs.

There are various approaches to reduce the hormonal response of cancer cells. Either biosynthetic enzyme inhibitors are used to reduce the biosynthesis of endogenous hormone or a better ligand to replace endogenous steroid hormone from binding with specific receptor. Sulfatase inhibitors and aromatase inhibitors are enzyme inhibitors while, antiestrogens are competitive inhibitors of estrogens. Antiprogestins have also been reported to act as antiproliferative agents. A brief account of steroidal anticancer agents has been shown in Fig. 2.

In the drug discovery, steroids have been a prime focus of research not only due to their fascinating structural framework [5], but also due to their astonishing array of pharmacological properties. Steroids have an excellent ability to penetrate cell membranes and bind to the nuclear and membrane receptors. Even a small change in steroid moiety can elicit an extensive biological response. All these facts have attracted Medicinal Chemists and Biochemists

UNCORRECTED PROOF

Please cite this article in press as: A. Gupta, et al., Current status on development of steroids as anticancer agents, J. Steroid Biochem. Mol. Biol. (2013), http://dx.doi.org/10.1016/j.jsbmb.2013.05.011

Download English Version:

https://daneshyari.com/en/article/8339124

Download Persian Version:

https://daneshyari.com/article/8339124

Daneshyari.com